

REVIEW ARTICLE

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Mechanisms of nasal hyper-reactivity

Abstract Hyper-reactivity to non-specific challenges has been considered a hallmark of asthma and is defined as an abnormal responsiveness of the bronchial airways to a variety of provocative agents. The mechanisms underlying hyper-reactivity in the upper and lower airways are not known. By using the nose to study the inflammatory response possible abnormalities can be investigated carefully and pathophysiology of specific airway hyper-reactivities can be better understood. Other factors than merely constriction of the bronchial smooth muscles can cause narrowing of the free lumen to airflow. Functionally different and very distinct mucosal end-organ reactivities may also be increased. If these reactivities can be well assessed, specific airway hyper-reactivity can be defined. In the present report, specific mucosal end-organ hyper-reactivities in the allergic nasal mucosa are presented. Certain widespread hypotheses, such as the role of the eosinophil and the “increased absorption permeability theory”, are disputed.

Key words Allergic rhinitis · Inflammation · Bronchial hyper-reactivity · Plasma exudation

Introduction

The nose provides excellent opportunities for studying functional aspects of inflammatory mucosal processes. The airway surface of the nose is readily accessible for well-controlled provocations with various kinds of stimuli, and mucosal responses can be equally well monitored by analysis of mucosal surface liquids, cells and biopsy specimens. Furthermore, several features of allergic and

inflammatory events may be similar in the nose and the tracheobronchial airways.

At present there is low accessibility of the tracheobronchial airways, an unknown and variable distribution of administered aerosols and lavage fluids, and a low recovery of administered lavage fluids [32]. Hence, results from bronchoalveolar lavage studies performed clinically must be interpreted with caution. The nose, however, as an integrated part of the airway mucosa, offers easy access to studies of the pathophysiological events of the human mucosal airways. The nasal mucosa shows striking similarities in structural and functional aspects to the tracheobronchial mucosa. The respiratory epithelium with the basement membrane, adjacent submucosa with micro vessels and glands have the same appearance in both locations. There are also data demonstrating that the nasal and tracheobronchial mucosa exhibit functional similarities in health and disease [31, 33, 35]. Nasal studies may thus serve to illustrate also pathophysiological events in the lower airways.

One important characteristic of inflammatory airway disease is the presence of hyper-reactivity. Non-specific bronchial hyper-responsiveness has been considered a hallmark of asthma [19], although it may not always be present and it may not always correlate with the inflammation present [21]. Hyper-reactivity of the bronchii is now defined as an abnormal responsiveness of the airways that is expressed as an increased obstruction of air flow on exposure to a variety of physical, chemical, and pharmacological provocative agents [8]. The mechanisms underlying hyper-reactivity in the upper and lower airways are not known. It has been suggested that abnormalities may exist in the permeability of the mucosa, in the smooth muscles or other tissue compounds. By using the nose to study the inflammatory response, many of the proposed abnormalities can be carefully investigated and pathophysiology of specific airway hyper-reactivities better understood. Factors other than merely constricting the bronchial smooth muscles can cause a narrowing of the free lumen for airflow. Furthermore functionally different and very distinct mucosal end-organ reactivities may be

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increased. If these reactivities can be assessed objectively specific airway hyper-reactivity can be defined. In the present article specific mucosal end-organ hyper-reactivities in the allergic nasal mucosa are presented. Certain hypotheses, such as the role of the eosinophil and the "increased absorption permeability theory," will be disputed.

The allergic-inflammatory nasal response

When allergen cross-links with two or more IgE molecules on the mast cell and basophil membrane in the nasal mucosa, the immediate allergic reaction is initiated. This reaction is characterized by the typical symptoms of sneezing, nasal blockage and secretion, and occurs within minutes after presentation of the antigen. The immediate allergic nasal reaction is then followed by a prolonged allergic inflammatory response and continued symptoms. In some individuals there is recurrence of symptoms and a repeated mucosal output of mediators and plasma [29]. The latter reaction has been termed the late nasal reaction. However, the prolonged allergic inflammatory response is functionally characterized by an increased mucosal reactivity to rechallenges with allergen ("specific challenge reactivity") or non-specific stimuli (such as histamine or methacholine) and an influx and activation of inflammatory cells into the superficial part of the nasal mucosa [28]. In previous studies we have tried to characterize allergen-induced nasal hyper-reactivity and investigated various relationships between inflammatory cells and the effects of anti-inflammatory pharmacotherapy on these processes. These studies were performed during experimental conditions in asymptomatic patients with allergic rhinitis during pollen-free winter months. Some studies were also undertaken during the natural course of hayfever, giving us the opportunity to validate previous results obtained during experimental challenges.

Nasal hyper-reactivity

Allergen-induced hyper-reactivity was described initially by Connel [9], who observed an increased nasal response to a rechallenge with allergen 24 h after the initial allergen challenge. This phenomenon was termed "priming." Later studies confirmed that a single allergen provocation during experimental challenges [5] as well as during exposure to natural allergens [7] could increase nasal mucosal reactivity to other stimuli. It has also been shown that increased reactivity in the nose may not only be an increased sensitivity to released mediators but can actually represent an exaggerated mucosal output of inflammatory mediators [30].

Furthermore, the hyper-reactivity seems to be a phenomenon exclusively related to the mucosa, since it can not be demonstrated at other sites in allergic individuals such as the skin [1, 3]. The presence of an increased nasal responsiveness to rechallenges with allergen after an initial provocation seems to be a common feature. Thus, in

an unselected population of asymptomatic patients with allergic rhinitis a majority responded with increased nasal symptoms and increased levels of *N*- α -tosyl-L-arginine methyl ester (TAME) – esterase in nasal lavage fluid as compared to the same pollen dose the day before. However, the presence and strength of the nasal hyper-reactivity could not be predicted by a standard skin prick test with relevant allergens [2]. Furthermore, the extent of the initial nasal response was not related to the presence and size of the allergen-induced hyper-reactivity. In contrast to the immediate allergic response, the allergen-induced hyper-reactivity was very susceptible to anti-inflammatory treatment. When a topical glucocorticoid was administered after the initial challenge and continued up to rechallenge 24 h later, the allergen-induced hyper-reactivity was abolished. These results demonstrate that allergen-induced hyper-reactivity is far more sensitive to glucocorticoid treatment than the immediate allergic response. This finding supports clinical observations of early glucocorticoid effects following initiation of treatment [4].

Inflammatory cells and hyper-reactivity

An attractive hypothesis has been widely disseminated in which the eosinophil has been proposed as responsible for the changes leading to increased airway reactivity. This hypothesis has been supported by results from in vitro studies showing that activated eosinophils are capable of releasing such toxic proteins as eosinophil cationic protein (ECP), major basic protein and eosinophil derived neurotoxin [12–14]. These proteins are believed to damage the epithelium and expose underlying sensory nerve endings. This hypothesis is further supported by a suggested link between the occurrence of late lower airway responses, increased lower airway reactivity and the local influx and activation of eosinophils into the tracheo-bronchial airway mucosa [11, 27]. These observations have been taken as evidence that the eosinophils play an active role in the genesis of airway hyper-reactivity. In the upper airways, however, where a more accurate analysis can be performed and repeated cell and mediator sampling can be undertaken during controlled conditions, it has not been possible to confirm the role of the eosinophil in the development of hyper-reactivity. A nasal challenge procedure was used to study tissue responses to allergen and included repeated methacholine challenges prior to and after the allergen challenge. Methacholine given topically to the nasal mucosa induces a glandular secretory response, allowing the volume of the induced secretions to be measured according to the technique described by Borum [6]. In nasal lavages performed immediately prior to each methacholine challenge, the total and relative number of eosinophils were counted and the levels of ECP measured as a marker of eosinophil activation. By 2 h of the allergen challenge, increased nasal secretory responsiveness to methacholine was demonstrable. At the same time-point the relative numbers of eosinophils were found increased in the lavage fluid studied. A correlation was

observed between the number of eosinophils and the levels of ECP in this fluid, suggesting that the harvested cells were activated. However, no specific relationship could be found between the number of eosinophils and the glandular secretory responsiveness. Thus some individuals demonstrated an early influx of eosinophils into the nasal mucosa and a later increase in glandular secretory reactivity and vice versa [23]. This finding suggests that the expression of airway mucosal inflammation, influx of eosinophils and secretory hyper-reactivity can happen at the same time but may not necessarily be linked to each other. Using a similar experimental challenge protocol with repeated methacholine challenges prior to and after different doses of topical intranasal pollen allergen, we found that weaker doses of allergen induced an increase in secretory reactivity [25]. The stronger doses of allergen resulted in an increase in secretory reactivity within 30 min after the immediate allergic reaction, while the number of eosinophils increased in nasal lavage fluid only 60 min after challenge, as determined by the increased level of ECP. These observations suggest that the hyper-reactivity found is not obligatorily linked to the presence of any so-called late-phase reaction, because such reactions occur several hours later. It has been suggested that the newer generation of non-sedating antihistamines may possess other properties in addition to blocking H₁ receptors in the nasal mucosa. The effect of two non-sedating antihistamines, terfenadine and cetirizine, on allergen-induced secretory hyper-reactivity and eosinophilia was studied in our laboratory. Cells and glandular secretory responses were calculated before and 24 h after nasal allergen challenge. We then found that both antihistamines reduced nasal secretory hyper-reactivity compared to placebo. The drugs, however, did not reduce the increased number of eosinophils 24 h after the immediate allergic reaction [24].

Possible mediators in hyper-reactivity

The cascade of events following allergen presentation to the airway mucosa leads to increased hyper-reactivity. Thus it seems possible to assume that one or several of the mediators released during the immediate allergic reaction could be responsible for the induction of this phenomenon. It has been shown previously that neither histamine nor methacholine increase any airway reactivity [18]. Platelet activating factor (PAF) is an inflammatory mediator that has been suggested to be responsible for inducing airway hyper-reactivity by recruiting eosinophils into the skin of atopic individuals [10, 20]. When PAF was applied topically to the nasal mucosa we found that it did not increase the glandular secretory reactivity, in contrast to allergen, but did actually possess a weak eosinophil chemotactic effect [22].

Different mucosal end-organ-hyper-reactivities

Knowledge of the pathophysiology of allergic rhinitis is based mainly on results achieved during laboratory challenge experiments. Until recently, very few studies addressed whether the pathophysiological changes and pharmacological effects achieved were also relevant under clinical conditions of disease. In a series of studies we monitored different aspects of the mucosal inflammatory response during the natural course of allergic rhinitis. In patients with active seasonal allergic rhinitis we found an increased mucosal output of both albumin and bradykinin harvested in nasal washings as an expression of both exudation of plasma proteins and activation of plasma protein systems with the formation of pro-inflammatory mediators [34]. Increased numbers of eosinophils and ECP were also observed on the nasal mucosal surface during natural disease [26]. These changes were accompanied by an increased secretory responsiveness of the nasal mucosa to methacholine and were also demonstrated during a very mild pollen season that did not produce any significant increases in actual symptoms. Both the increases in the number and activation of eosinophils as well as the increased secretory responsiveness to methacholine were significantly inhibited by topical administration of glucocorticoids [26]. Although pollen exposure diminishes at the end of pollen season, patients still have more pronounced symptoms and experience more nasal complaints at this time than had earlier in the season in response to the same pollen amount [17]. This finding suggests the presence of a naturally acquired hyper-reactivity to allergen. At the end of birch-pollen season we were also able to demonstrate an increased vascular exudative response to histamine when compared to the same histamine dose at a symptom-free time outside the season [15]. In unpublished studies, we found an increased sensory neural reactivity during naturally occurring allergic disease. Capsaicin, a neurogenic compound that stimulates release of neuropeptides from sensory nerve endings, was applied to the nasal mucosa at the end of the pollen season. Patients with active allergic rhinitis experienced a more intense pain in the nose than had before pollen season. A neurogenic stimulus may produce an increased secretory response, but capsaicin-induced neurogenic inflammation (with plasma exudation) did not occur in the human airway, even during conditions of active allergic rhinitis.

Mucosal hyperpermeability

The different mucosal end-organ reactivities cannot be explained by an increased absorption permeability of the nasal mucosa. Late into the pollen season when patients showed an increased responsiveness to low pollen exposure, absorption of a radioactive tracer (⁵¹Cr-EDTA) across the nasal mucosa was significantly lower than that found some weeks prior to the allergic season when patients were asymptomatic [16]. Studies carried out during

naturally occurring allergic rhinitis demonstrated an increased mucosal exudation of plasma, secretory, sensorineural, and vascular exudative hyper-reactivity, as well as an increased number and activation of both mast cells and eosinophils but a reduced absorption permeability.

Conclusions

Allergen-induced nasal hyper-reactivity is a common and important feature of the inflammatory processes affecting the airway mucosa. However, the underlying pathophysiological mechanisms leading to increased airway reactivity are still obscure. Our results have questioned any clear-cut links between late-phase reactions, influx and activation of eosinophils and development of hyper-reactivity. We now propose that the inflammatory mucosa is functionally characterized by different specific end-organ hyper-reactivities. This hyper-responsiveness cannot be explained by increased mucosal penetration of allergens or challenging agents, but may rather reflect an increased release of cellular mediators and increased sensitivity of specific mucosal end-organs.

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